AF/1633
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Date of Signature and Deposit : September 11, 2000

Carl R. Schwartz, Reg. No. 29,437

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

Applicant : James A. Thomson
Art Unit : 1633
Serial No.: 09/106,390
Filed : June 26, 1998
Examiner : D. Clark
Title : Primate Embryonic Stem Cells

Transmittal Of Appellant's Appeal Brief

Commissioner For Patents
Washington, D.C. 20231
Attention: Bd. Pat. App./Inf.

Dear Sir:

Enclosed are three copies of Appellant's Brief on Appeal. The $300.00 fee for filing the brief and any other fees required in this application should be charged to Deposit Account No. 17-0055.

Respectfully submitted,

James A. Thomson

Dated: September 11, 2000 By: _____

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Serial No.	:	09/106,390
Filed	:	June 26, 1998
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Title	:	PRIMATE EMBRYONIC STEM CELLS

APPELLANT'S BRIEF ON APPEAL

Commissioner for Patents
Washington, D.C. 20231
Attention: Bd. Pat. App./Inf.

Dear Sir:

Appellant, having filed a timely Notice of Appeal on July 12, 2000 in the above-identified patent application, hereby submits this appeal brief (in triplicate).

I. REAL PARTY IN INTEREST

This application has been assigned to the Wisconsin Alumni Research Foundation (a licensing representative for the University of Wisconsin at Madison), a Wisconsin corporation having a place of business in Madison, Wisconsin. That company has granted licenses under the application to its affiliate WiCell Research Institute, Inc., a Wisconsin corporation having a place of business in Madison, Wisconsin and to Geron Corp., a California corporation having a place of business in Menlo Park, California.

II. RELATED APPEALS AND INTERFERENCES

There are no related interferences. There are also no currently pending related appeals.

III. STATUS OF CLAIMS

Claims 1-11 are currently pending (see Appendix A attached hereto). They stand rejected only under § 112, first paragraph, for lack of enablement. This appeal is taken with respect to all of these claims (claims 1-11).

IV. STATUS OF AMENDMENTS

A final action issued on January 14, 2000. Responsive remarks (without any proposed amendments) were filed after a telephone interview by the undersigned on March 13, 2000. An Advisory Action issued on June 26, 2000 which maintained the rejection.

V. SUMMARY OF THE INVENTION

The invention relates to stable human embryonic stem cell lines having highly desired characteristics, methods of making them, and methods of maintaining them in an undifferentiated state. These cell lines have been shown to differentiate, when desired, to varied cell types (e.g. endoderm, mesoderm and ectoderm). They are useful in connection with drug discovery and medical treatments, and for studies of human developmental biology.

The enclosed NIH funding guidelines, recently published at 65 Fed. Reg. 51976 on August 25, 2000, are in significant part a result of the present invention. They specify guidelines of how U.S. government support can be obtained for research using these stem cells. These guidelines also note that human embryonic stem cells have "enormous potential" for the development of new therapies "for the most devastating diseases", and also describe a number of other reasons why such cells and their uses are of such great importance.

VI. ISSUE

There is only one issue which underlies the final rejection. It is whether (for purposes of § 112, first paragraph) a human embryonic stem cell line must be shown to have "germ line competence" in order to establish that a human embryonic pluripotent cell line can be properly be referred to as being a human embryonic stem cell line.

The Office Action appears to contend that to establish the existence of a "human embryonic stem cell" the cells would need to be implanted into a blastocyst, allowed to grow to term (presumably a recombinant live human would be born), and then Applicant would need to demonstrate the human to have mosaicism in the germ line (presumably the human would have to grow up, mate, and have a child who receives the specified trait).

Apparently then the Office Action is taking the position that a human embryonic stem cell is necessarily a "totipotent" cell, and is thus even precluding the Applicant from adopting any other definition. In contrast, Applicant (and, it is submitted, the art) use the term to refer to a pluripotent cell, e.g. capability of differentiating into specified human tissues, regardless of also having the capability to create a functional embryo or pass traits to progeny. Thus, it is contended that proof of germ line competency is not required to confirm that a human embryonic stem cell has been created in the present case.

VII. GROUPING OF CLAIMS

For purposes of the above, claims 1-11 may be considered to present a single group (with claim 1 being representative).

VIII. ARGUMENT

In the final Office Action dated January 14, 2000 the Examiner acknowledged that Applicant had developed pluripotent human embryonic cells capable of differentiation into derivates of all three embryonic germ layers cells. The only remaining issue was therefore whether, in the context of "human embryonic stem cells", there must be a showing of germ line competence in order to confirm that a human embryonic stem cell, rather than "just" a human embryonic pluripotent cell, had been created.

The Examiner has contended that there is an established definition of embryonic stem cells in the mouse art that requires germ line competence, and that therefore the art would find a definition of human embryonic stem cells that did not require this attribute to be repugnant. The Examiner also has contended that Applicant has admitted in the specification that germ line competence is required for human embryonic stem cells, and that in any event, Applicant's attempt to establish his own definition in the application specification was not a sufficiently clear attempt to create a definition. Applicant respectfully disagrees with each of these contentions.

A. The Accepted Definition In The Art

The art has adopted a definition of "human embryonic stem cell" that does not require proof of germ line competence. In J. Thomson et al., 282 Science 1145-1147 (1998), a peer

reviewed publication of record, the term "human embryonic stem cell" was accepted by the publisher and the peer review committee, notwithstanding the statement therein that germ line competence was not a required attribute.

This argument was made in the response after final. The Advisory Action did not directly respond to this argument.

Various other researchers have accepted this definition as well. See e.g. J. Rossant et al., 17 Nature Biotechnology 23-24 (1999); J. Gearhart, 282 Science 1061-1062 (1998); A. Chapman et al., Stem Cell Research And Applications Monitoring The Frontiers Of Biomedical Research, American Association for the Advancement of Science and Institute for Civil Society (November, 1999). For example, at page 24 of the Rossant et al. article, the following appears:

> ...the ability to contribute to all cell types, including the germ line, in a chimera -- is not applicable to humans [emphasis added]

This argument was made in the response after final. The Advisory Action did not specifically address it.

Very recently the NIH also acknowledged how the art is using various of these terms. In this regard, on page 51979, the term "human pluripotent stem cells" was noted as being technically known as "human embryonic stem cells". The equivalent to "human embryonic stem cells" was not stated to be human totipotent stem cells.

The rest of the recited NIH definition for the human embryonic stem cells was "cells that are self-replicating, are derived from human embryos or human fetal tissue, and are known to develop into cells and tissues of the three primary germ layers." The Office has not contested that Applicant's human embryonic stem cells have those characteristics.

Applicant's counsel called the Examiner to note the inconsistency between the position of the last Office Action regarding what is the accepted definition in the art, and what the NIH believes it is. The Examiner indicated that she had reviewed the guidelines, yet found other aspects of the guidelines supportive of the Office's view (albeit she did not specify what they were). In any event, the undersigned respectfully contends that nothing in the guidelines supports

the Office Action rejection, and that the guidelines strongly support Applicant's position.

In sum, Applicant has submitted evidence of acceptance by a U.S. government agency, and by researchers, of a definition of "human embryonic stem cells" that does not require germ line competency. To date the Office has not cited any publication that asserts that germ line competency, in the context of human embryonic stem cells, is required for there to be a human embryonic stem cell. This alone should be sufficient to overturn the rejection.

B. Applicant Has Not Admitted On Page 1 Of The Specification That Totipotency Is Required

The Advisory Action asserted that "The term 'embryonic stem cells' includes the property of germ-line competency as stated in the specification at page 1 lines 24-25". However, that portion of Applicant's specification is in the context of a prolonged discussion of prior developments relating to mouse ES, and in any event actually states:

> ...Embryonic stem (ES) cells are derived from the embryo and are pluripotent, thus possessing the capability of developing into any organ or tissue type or, at least potentially, into a complete embryo. [emphasis added]

Note the use of "pluripotent", not "totipotent". As noted on page 33 of the Chapman et al. article of record (glossary section), a totipotent cell can give rise to virtually any tissue type or even a functional cell. A pluripotent cell can give rise to virtually any tissue type, but not necessarily "to a functioning organism". Thus, the lines cited by the Examiner contain language contrary to the Office's interpretation, and in any event was not meant in the manner that it is being construed.

There is nothing in this specification excerpt that is tied to human ES, much less describing germ line competency as a stem cell definitional requirement, or describing the attribute of ability to grow up a complete human from the cells, mate the human, and pass to children a trait introduced via the stem cell. Moreover, even with respect to growing up the first mouse in recombinant form, the quoted language never

imposes the requirement of ability to create even the first embryo as a condition of using the term (note the word "potentially").

C. Even Mouse Embryonic Stem Cells Do Not Need To Be Germ Line Competent

The final rejection also relied on a Nichols et al. reference for a definition of embryonic stem cells which purportedly required germ-line-competence. However, Nichols et al. said nothing about what the term meant in the context of human embryonic stem cells. Instead, it is related to mouse embryonic stem cells.

Even in the context of mouse embryonic stem cells the Nichols et al. reference did not define the term as including germ line competency. In fact, the title of the Nichols et al. article included the term "germ-line-competent embryonic stem (ES) cells". It was pointed out by Applicant that if the definition of embryonic stem cell in the mouse already included germ line competency, there would be no reason to use the words "germ line competent" in the title.

Further, the first sentence of the introduction of Nichols et al. defined mouse ES cells as "permanent cell lines established directly from the inner cell mass of the pre-implantation mouse embryo" citing the definition of Martin (who coined the term as applied to the mouse). The record already includes a copy of the Martin article, G. Martin, 78 P.N.A.S. USA 7634-7638 (1981). Martin specifically noted on page 7635 her rationale for why she chose the term:

> Such cells were termed embryonic stem cells (ESC) to denote their origin directly from embryos and to distinguish them from embryonal carcinoma cells (ECC)...

There is no assertion in the Martin article of germ line competence, or anything in the specified Martin definition to require this attribute, and we are not aware of the Martin line ever even having been reported to have this feature.

The final Office Action apparently relied mostly on the next two sentences of the introduction of Nichols et al. which stated that:

> They retain the ability to participate in normal embryonic development and, following reintroduction to the blastocyst, they generate chimaeric animals that are mosaic in all their tissues. Mosaicism extends to the germ cell lineage and ES cells can contribute fully functional gametes (Bradley et al. 1984).

However, even for mice, this was not an attempt to redefine what an ES cell was. It was merely a recognition that Bradley et al. had developed a mouse line which had this attribute. This can be better understood by comparing the discussion at page 1347 of the Nichols et al. article, column 1, where it was acknowledged that:

> Other workers have reported that not all ES lines differentiate normally and relatively few exhibit high levels of germ-line transmission [citing other Martin articles]

Thus, contrary to what it is cited for, Nichols et al. did not purport to redefine what a mouse embryonic stem cell was.

The Advisory Action did not specifically respond to the above argument which was made in the response after final.

D. Applicant Has The Right To Be His Own Lexicographer

Applicant had also argued that at minimum the record established that his definition is not repugnant to the art (regardless of whether it was widely accepted). Applicant is fully entitled to adopt and use a definition that does not require germ line competence. M.P.E.P. § 2173.01 states:

> A fundamental principle contained in 35 U.S.C. 112, second paragraph is that applicants are their own lexicographers. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as the terms are not used in ways that are contrary to accepted meanings in the art.

At page 7, beginning line 10 of the specification, a definition of ES cells was provided which did not require germ line competency:

> True ES cells should: (i) be capable of indefinite proliferation in vitro in an undifferentiated state; (ii) maintain a normal karyotype through prolonged culture; and (iii) maintain the potential to differentiate to derivatives of all three embryonic germ layers (endoderm, mesoderm, and ecoderm) even after prolonged culture.

Applicant is entitled to use this definition because (as noted above) it is not contrary to any well accepted meaning in the art for human embryonic stem cells. In fact, as noted above, Applicant is using the accepted definition for human embryonic stem cells.

The Office's response to this contention in an interview summary was that the phraseology "True ES cells should" was not a clear enough statement that this was intended as a definition. However, page 8 of the specification begins with the following quotation:

> ...The primate ES cell lines are true ES cell lines in that they (i) are capable of indefinite proliferation in vitro in an undifferentiated state; (ii) are capable of differentiation to derivatives of all three embryonic germ layers (endoderm, mesoderm, and ectoderm) even after prolonged culture; and (iii) maintain a normal karyotype throughout prolonged culture. The true primate ES cells lines are therefore pluripotent.

In a situation where a patent applicant has elected to be a lexicographer by providing an explicit definition in the specification for a claim term which is not repugnant to the art, the definition selected by the patent applicant controls so long as it is appears "in some manner". In re Paulsen, 30 F.3d 1475, 31 U.S.P.Q.2d 1671, 1674 (Fed. Cir. 1994). Nothing requires an applicant to use the magic word "definition" in the specification to cause something to be understood to be a definition.

E. The Office Action Has Not Established A Pattern Of Unpredictability Relating To Germ Line Competency Once Stable Isolation Of A Pluripotent Embryonic Cell Has Been Accomplished

While the above discussion should be sufficient to overcome the rejection, it should be noted that there is nothing of record to establish that Applicant's cell lines do not have the germ line competency attribute. The Office Action merely asserts that the art of isolating ES cells is so highly unpredictable that Applicant should need to prove this attribute (if germ line competency is part of the definition).

However, the Office admits that Applicant has stably isolated the stable human and non-human embryonic pluripotent cell lines. Thus, any unpredictability relating to isolation is not an issue here. Further, the Office Action notes that germ line competency has been found in mice after isolation of pluripotent ES cells. There is nothing of record to establish a consistent pattern of failure in varied species to establish germ line competency once stable pluripotent embryonic cells are isolated.

F. Public Policy Implications

Finally, the policy implications of the Office Action's position should also be considered. In essence, the Office Action would condition patent protection on evidence that the invention will work to create live recombinant humans. There is unlikely to be any practical utility in the U.S. to the creation of a live recombinant human due to the ethical, moral, and legal constraints relating thereto. Moreover, encouraging such experimentation would run counter to the careful balancing of ethical and moral concerns reflected by the enclosed NIH guidelines.

Conclusion

In view of the above, it is respectfully requested that the rejection be overturned. The Board is hereby authorized to charge the $300 appeal brief fee to Deposit Account 17-0055, together with any other fees that may be required in this appeal.

Respectfully submitted,
James A. Thomson

Dated: September 11, 2000 By: _____

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APPENDIX A

Claims of Patent Application Serial No. 09/106,390

1. A purified preparation of human embryonic stem cells which (i) will proliferate in an *in vitro* culture for over one year, (ii) maintains a karyotype in which the chromosomes are euploid and not altered through prolonged culture, (iii) maintains the potential to differentiate to derivatives of endoderm, mesoderm, and ectoderm tissues throughout the culture, and (iv) is inhibited from differentiation when cultured on a fibroblast feeder layer.

2. The preparation of claim 1, wherein the stem cells will spontaneously differentiate to trophoblast and produce chorionic gonadotropin when cultured to high density.

3. A purified preparation of human embryonic stem cells wherein the cells are negative for the SSEA-1 marker, positive for the SSEA-4 marker, express alkaline phosphatase activity, are pluripotent, and have euploid karyotypes and in which none of the chromosomes are altered.

4. The preparation of claim 3, wherein the cells are positive for the TRA-1-60, and TRA-1-81 markers.

5. The preparation of claim 3, wherein the cells continue to proliferate in an undifferentiated state after continuous culture for at least one year.

6. The preparation of claim 3, wherein the cells will differentiate to trophoblast when cultured beyond confluence and will produce chorionic gonadotropin.

7. The preparation of claim 3, wherein the cells remain euploid for more than one year of continuous culture.

8. The preparation of claim 3, wherein the cells differentiate into cells derived from mesoderm, endoderm and ectoderm germ layers when the cells are injected into a SCID mouse.

9. A method of isolating a human embryonic stem cell line, comprising the steps of:

(a) isolating a human blastocyst;

(b) isolating cells from the inner cell mass of the blastocyte of (a);

(c) plating the inner cell mass cells on embryonic fibroblasts, wherein inner cell mass-derived cell masses are formed;

(d) dissociating the mass into dissociated cells;

(e) replating the dissociated cells on embryonic feeder cells;

(f) selecting colonies with compact morphologies and cells with high nucleus to cytoplasm ratios and prominent nucleoli; and

(g) culturing the cells of the selected colonies to thereby obtain an isolated human embryonic stem cell line.

10. A method as claimed in claim 9, further comprising maintaining the isolated cells on a fibroblast feeder layer to prevent differentiation.

11. A cell line developed by the method of claim 9.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells

SUMMARY: The National Institutes of Health (NIH) is hereby publishing final "National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells." The Guidelines establish procedures to help ensure that NIH-funded research in this area is conducted in an ethical and legal manner.

EFFECTIVE DATE: These Guidelines are effective on August 25, 2000. The moratorium on research using human pluripotent stem cells derived from human embryos and fetal tissue put in place by the Director, NIH, in January 1999, will be lifted on August 25, 2000.

SUMMARY OF PUBLIC COMMENTS ON DRAFT GUIDELINES: On December 2, 1999 (64 FR 67576), the NIH published Draft Guidelines for research involving human pluripotent stem cells (hPSCs) in the **Federal Register** for public comment. The comment period ended on February 22, 2000.

The NIH received approximately 50,000 comments from members of Congress, patient advocacy groups, scientific societies, religious organizations, and private citizens. This Notice presents the final Guidelines together with NIH's response to the substantive public comments that addressed provisions of the Guidelines.

Scope of Guidelines and General Issues

Respondents asked for clarification of terminology used in the Guidelines and some commented that the language was not appropriate or was too technical, particularly the informed consent sections. The NIH agrees that these Guidelines should be clear and understandable. Changes, including some reorganization of the sections, were made to this end. The Guidelines are written primarily for the purpose of informing investigators of the conditions that must be met in order to receive NIH funding for research using hPSCs and, therefore, some technical language is required. The Guidelines do not define the precise language that should appear in informed consent documents because these should be developed by the investigator/clinician specifically for a particular study protocol or procedure for which the consent is being sought. Existing regulatory provisions require (45 CFR 46.116) that the language in informed consent documents be understandable to prospective participants in the study.

Respondents suggested that NIH funding for research using hPSCs would be in violation of the DHHS appropriations law and that derivation of hPSCs cannot be distinguished from their use. For this reason, a number of respondents asked that the NIH withdraw the draft Guidelines. The NIH sought the opinion of the DHHS General Counsel, who determined that "federally funded research that utilizes hPSCs would not be prohibited by the HHS appropriations law prohibiting human embryo research, because such cells are not human embryos." Comments questioning this conclusion did not present information or arguments that justify reconsideration of the conclusion.

Respondents commented that the Guidelines are too restrictive or that there is no need for Federal Guidelines for this arena of research. Comments asserted that federally funded research using hPSCs should go forward without formal requirements, in the same manner as in the private sector. In order to help ensure that the NIH-funded research using hPSCs is conducted in an ethical and legal manner, the NIH felt it was advisable to develop and implement guidelines. To this end, the NIH Director convened a Working Group of the Advisory Committee to the Director, NIH (ACD), to advise the ACD on the development of guidelines and an oversight process for research involving hPSCs. The NIH Director charged the Working Group with developing appropriate guidelines to govern research involving the derivation and use of hPSCs from fetal tissue and research involving the use of hPSCs derived from human embryos that are in excess of clinical need.

Respondents commented regarding the sources of stem cells. Some respondents stated that research on hPSCs was unnecessary because stem cells from adults, umbilical cords, and placentas could be used instead. Other respondents asked the NIH to restrict Federal funding for hPSC research to those cells derived from fetal and adult tissue but not embryos. Other respondents asked that the Guidelines encompass research using stem cells from adult tissues.

As stated under Section I. *Scope of Guidelines*, the Guidelines apply to the use of NIH funds for research using hPSCs derived from human embryos or human fetal tissue. The Guidelines do not impose requirements on Federal funding of research involving stem cells from human adults, umbilical cords, or placentas.

Given the enormous potential of stem cells to the development of new therapies for the most devastating diseases, it is important to simultaneously pursue all lines of promising research. It is possible that no single source of stem cells is best or even suitable/usable for all therapies. Different types or sources of stem cells may be optimal for treatment of specific conditions. In order to determine the very best source of many of the specialized cells and tissues of the body for new treatments and even cures, it is vitally important to study the potential of adult stem cells for comparison to that of hPSCs derived from embryos and fetuses. Unless all stem cell types are studied, the differences between adult stem cells and embryo and fetal-derived hPSCs will not be known.

Moreover, there is evidence that adult stem cells may have more limited potential than hPSCs. First, stem cells for all cell and tissue types have not yet been found in the adult human. Significantly, cardiac stem cells or pancreatic islet stem cells have not been identified in adult humans.

Second, stem cells in adults are often present in only minute quantities, are difficult to isolate and purify, and their numbers may decrease with age. For example, brain cells from adults that may be neural stem cells have been obtained only by removing a portion of the brain of an adult with epilepsy, a complex and invasive procedure that carries the added risk of further neurological damage. Any attempt to use stem cells from a patient's own body for treatment would require that stem cells would first have to be isolated from the patient and then grown in culture in sufficient numbers to obtain adequate quantities for treatment. This would mean that for some rapidly progressing disorders, there may not be sufficient time to grow enough cells to use for treatment.

Third, in disorders that are caused by a genetic defect, the genetic error likely would be present in the patient's stem cells, making cells from such a patient inappropriate for transplantation. In addition, adult stem cells may contain more DNA abnormalities caused by exposure to daily living, including sunlight, toxins, and errors made during DNA replication than will be found in fetal or embryonic hPSCs.

Fourth, there is evidence that stem cells from adults may not have the same capacity to multiply as do younger cells. These potential weaknesses may limit the usefulness of adult stem cells.

Respondents were concerned that these are guidelines and not requirements or regulations. Although these are guidelines and not regulations, they prescribe the documentation and assurances that must accompany requests for NIH funding for research utilizing hPSCs. If the funding requests do not contain the prescribed information, funding for hPSC research will not be provided. Compliance with the Guidelines will be imposed as a condition of grant award.

Respondents commented that there had not been enough widespread public disclosure/discussion of this research or the Guidelines. Prior to the development of draft Guidelines, there were two Congressional hearings on hPSCs. In a further effort to ensure substantial discussion and comment, the NIH convened a Working Group of the Advisory Committee to the Director, NIH (ACD), to advise the ACD on the development of these Guidelines. The Working Group was composed of scientists, patients and patient advocates, ethicists, clinicians, and lawyers. The Working Group met in public session on April 8, 1999, and heard from members of the public, as well as professional associations and Congress. In developing the draft Guidelines, the NIH also considered advice from the National Bioethics Advisory Commission (NBAC). Draft Guidelines were published for public comment in the **Federal Register** on December 2, 1999, for 60 days, and, in response to public interest, the comment period was extended an additional 28 days. Approximately 50,000 comments were received. NIH issued a national press release announcing the **Federal Register** notice and many of the Nation's newspapers carried articles on this area of research and on the Guidelines. Patient groups, scientific societies, and religious organizations convened meetings and discussion groups and disseminated materials about this area of research and about the Guidelines.

Comment was received about whether the Guidelines apply to hPSC lines developed outside of the United States. The Guidelines make no distinction based upon the country in which an hPSC line is developed. All lines to be used in hPSC cell research funded by NIH must meet the same requirements.

Derivation and Use of hPSCs From Fetal Tissue

Respondents made the point that the NIH has specified certain requirements for the use of human fetal tissue to derive hPSCs in addition to those imposed on other areas of human fetal tissue research. These respondents suggested that the section of the Guidelines pertaining to fetal tissue sources be omitted. In order to ensure uniformity in NIH's oversight of research using hPSCs, the Guidelines were extended to govern hPSCs derived from both human embryos and fetal tissue.

Use of hPSCs Derived From Human Embryos

Respondents suggested that the Guidelines refer to "fertility treatment" rather than to "infertility treatment" in order to clarify that they allow the use of human embryos from treatments that employ assisted reproductive technologies to facilitate reproduction in fertile, as well as in infertile, individuals. The Guidelines have been changed accordingly.

Respondents suggested dropping the word "early" throughout the document or more clearly defining "early." The word "early" in reference to human embryos has been deleted; the Guidelines make it clear that NIH funding of research using hPSCs derived in the private sector from human embryos can involve only embryos that have not reached the stage at which the mesoderm is formed.

Some respondents were concerned that embryos might be created for research purposes. Other respondents stated there should be no distinction between embryos created for research purposes and those created for fertility treatment. Investigators seeking NIH funds for research using hPSCs are required to provide documentation, prior to the award of any NIH funds, that embryos were created for the purposes of fertility treatment. President Clinton, many members of Congress, the NIH Human Embryo Research Panel, and the NBAC have all embraced the distinction between embryos created for research purposes and those created for reproductive purposes.

Respondents were concerned about the creation of a "black market" for human embryos, and expressed concerns that individuals will be coerced into donating embryos. The Guidelines state that there can be no incentives for donation and that a decision to donate must be made free of coercion. In addition, the Guidelines set forth conditions that will help ensure all donations are voluntary. For example, with regard to hPSCs derived from embryos, research using Federal funds may only be conducted if the cells were derived from frozen embryos that were created for the purpose of fertility treatment and that were in excess of clinical need.

Respondents commented on the requirement that human embryos be frozen in order to qualify for derivation of hPSCs to be used in NIH-funded research. Respondents suggested that the freezing requirement would preclude the use of hPSCs derived from embryos that are genetically and chromosomally abnormal, since such embryos are usually not frozen for reproductive purposes. While the NIH acknowledges that research on hPSCs derived from such embryos could yield important scientific information, limiting research to hPSCs derived from frozen human embryos will help ensure that the decision to donate the embryo for hPSC research is distinct and separate from the fertility treatment.

Financial Issues

Respondents expressed concern regarding the sale of fetal tissue for profit and whether hPSC research would encourage such activity. Respondents also were concerned about whether clinics or doctors would profit from the derivation of hPSCs and/or their sale. Section 498B of the Public Health Service Act prohibits any individual from knowingly acquiring or selling human fetal tissue for "valuable consideration." In addition, the Guidelines prohibit any inducement for the donation of human embryos for research purposes. The Guidelines also call for an assurance that the hPSCs to be used in NIH-funded research were obtained through a donation or through a payment that does not exceed the reasonable costs associated with the transportation, processing, preservation, quality control and storage of the hPSCs. All grantees must sign an assurance that they are in compliance with all applicable Federal, State, and local laws. Each funded research institution is responsible for monitoring compliance by individual investigators with any such applicable laws.

Respondents questioned the prohibition against embryo donors benefitting financially from their donation. This clause was retained in the final Guidelines to help ensure that the donating individuals are offered no inducements to donate and that all donations are voluntary.

Respondents suggested that the Guidelines be strengthened to include a waiver of intellectual property rights. This proposed change would be inconsistent with 45 CFR 46.116 of the regulation for the protection of human subjects of research, which provides that no informed consent may include

language through which the subject waives or appears to waive any of the subject's legal rights.

Respondents questioned the reference in the requirements for informed consent related to the commercial potential of donated material. The paragraphs providing for disclosure in the informed consent of the possibility that the donated material could have commercial potential were modified. The reference in these paragraphs to "donated material" did not accurately reflect the intent of the provision. The Guidelines now make clear that the "results of research on the human pluripotent stem cells may have commercial potential."

Ineligible Research

Respondents objected to the areas of research that the NIH has deemed ineligible, particularly research that is not restricted by statute or regulation, such as research utilizing hPSCs that were derived using somatic cell nuclear transfer, i.e., the transfer of a human somatic cell nucleus into a human egg. The NIH determined that, at this time, research using hPSCs derived from such sources has not received adequate discussion and consideration by the public and is, therefore, ineligible for NIH funding.

Separation of Fertility Treatment and Abortion From Research

Respondents were concerned that hPSC research would encourage abortion. The law and the Guidelines guard against encouraging abortion by requiring that the decision to have an abortion be made apart from and prior to the decision to donate tissue.

Respondents objected to the condition in the Guidelines that the fertility physician could not be the same person as the researcher deriving stem cells. Some respondents stated that the Institutional Review Board (IRB) or an independent physician would be able to guard against this conflict of interest. The restriction was designed so that the person treating the individuals seeking fertility treatment, who is involved in decisions such as how many embryos to produce, is not the person seeking to derive hPSCs. This separation will help ensure that embryos will not be created in numbers greater than necessary for fertility treatment.

Respondents suggested that the clauses regarding donation of fetal tissue or human embryos for derivation of stem cells for eventual use in transplantation be changed explicitly to prevent directed donation. This change has been made.

Identifiers

Respondents were concerned about removing identifiers. There was concern that the investigator would not be able to document compliance with the Guidelines requirements without identifiers, or that the removal of identifiers would make it impossible to conduct certain genetic studies or develop therapeutic materials. The Guidelines have been modified to clarify that the term "identifier" refers to any information from which the donor(s) can be identified, directly or through identifiers linked to the donors. However, since information identifying the donor(s) may be necessary if the tissue or cells are to be used in transplantation, the Guidelines have also been modified to state that the informed consent should notify donor(s) whether or not identifiers will be retained.

Respondents commented that DNA is an identifier and that all donors of human embryos or fetal tissue should be told that identifiers such as DNA will be retained with the samples. Although DNA can be used to determine the individual from whom a tissue sample was taken, this can be done only when one has a sample from both the tissue in question and the putative donor; it cannot be used to identify an individual out of a population. Moreover, it is difficult to identify a donor using tissue derived from a fetus or embryo, since the tissue is not genetically identical to the donor.

Informed Consent and IRB Review

Respondents asked why investigators were expected to provide documentation of IRB review of derivation from human embryos, but not for derivation from fetal tissue. Respondents suggested that the requirements be changed so that protocols for both sources of hPSCs must be approved by an IRB. The Guidelines have been changed to make clear that the IRB review requirements regarding the derivation of cells from fetal tissue and human embryos are the same.

Comment was received expressing concern that the informed consent explicitly state that the donor will have no dispositional authority over derived pluripotent stem cells. The Guidelines state that donation of human embryos should have been made without any restriction regarding the individual(s) who may be the recipient of the cells derived from the hPSCs for transplantation. Such a statement is consistent with the statutory provision applicable to the donor informed consent for the use of fetal tissue for transplantation. The Guidelines now provide for the inclusion of a statement to this effect in the informed consent.

Respondents urged that the Guidelines be revised to remove the prohibition on potential donors receiving information regarding subsequent testing of donated tissue in the situation when physicians deem disclosure to be in the donors' best interest. This change has been made.

Respondents requested clarification regarding the persons from whom consent for donation of embryos for research must be obtained. The Guidelines call for informed consent from individual(s) who have sought fertility treatment. Only the individual(s) who were part of the decision to create the embryo for reproductive purposes should have been part of the decision to donate for the derivation of hPSCs.

Respondents urged that fertility clinics should be able to discuss with patients the option of donating embryos for research at the beginning of the IVF process. The Guidelines do not delineate the timeframe during which the general option of donating embryos for research can be discussed. However, according to the Guidelines, obtaining consent for donation of embryos for the purpose of deriving hPSCs should not occur until after the embryos are determined to be in "excess of clinical need."

Oversight

Respondents stated that the NIH's oversight in this area of research was very important to the legal and ethical conduct of this research, and asked for more information regarding the oversight process. Information about the operations of the Human Pluripotent Stem Cell Review Group (HPSCRG) can be found in the final Guidelines and on the NIH Web page.

Respondents were concerned about whether and how NIH would monitor research after a researcher receives NIH funds. Compliance with the Guidelines will be largely determined prior to the award of funds. Follow-up to ensure continued compliance with the Guidelines will be conducted in the same manner as for all other conditions of all other NIH grant awards. It is the responsibility of the investigator to file progress reports, and it is the responsibility of the funded institution to ensure compliance with the NIH Guidelines. NIH staff will also monitor the progress of these investigators as part of their regular duties.

Respondents asked about penalties for not following the Guidelines. The following actions may be taken by the NIH when there is a failure to comply with the terms and conditions of any award: (1) Under 45 CFR 74.14, the NIH can impose special conditions on an award, including increased oversight/monitoring/reporting requirements for an institution, project or investigator; and (2) under 45 CFR 74.62, if a grantee materially fails to comply with the terms and conditions of the award, the NIH may withhold funds pending correction of the problem or, pending more severe enforcement action, disallow all or part of the costs of the activity that was not in compliance, withhold further awards for the project, or suspend or terminate all or part of the funding for the project. Individuals and institutions may be debarred from eligibility for all Federal financial assistance and contracts under 45 CFR Part 76 and 48 CFR Subpart 9.4, respectively. Because these sanctions pertain to all conditions of grant award, the NIH did not reiterate them in the Guidelines.

Respondents suggested that the HPSCRG hold periodic Stem Cell Policy Conferences (similar to the Gene Therapy Policy Conferences conducted by the Recombinant DNA Advisory Committee ("RAC")) in order to solicit and consider public comment from interested parties on the scientific, medical, legal, and ethical issues arising from stem cell research. Members of the HPSCRG will serve as a resource for recommending to the NIH any need for Human Pluripotent Stem Cell Policy Conferences.

Other Changes

Because compliance materials may be made public prior to funding decisions, we have added a sentence requiring the principal investigator's written consent to the disclosure of such material necessary to carry out public review and other oversight procedures.

The draft Guidelines required HPSCRG review of proposals from investigators planning to derive hPSCs from fetal tissue. Because the Guidelines address proposals for NIH funding for the use of hPSCs, this requirement has been removed from the Guidelines.

The text of the final Guidelines follows.

National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells

I. Scope of Guidelines

These Guidelines apply to the expenditure of National Institutes of Health (NIH) funds for research using human pluripotent stem cells derived from human embryos (technically known as human embryonic stem cells) or human fetal tissue (technically known as human embryonic germ cells). For purposes of these Guidelines, "human pluripotent stem cells" are cells that are self-replicating, are derived from human embryos or human fetal tissue, and are known to develop into cells and tissues of the three primary germ layers. Although human pluripotent stem cells may be derived from embryos or fetal tissue, such stem cells are not themselves embryos. NIH research funded under these Guidelines will involve human pluripotent stem cells derived: (1) From human fetal tissue; or (2) from human embryos that are the result of *in vitro* fertilization, are in excess of clinical need, and have not reached the stage at which the mesoderm is formed.

In accordance with 42 Code of Federal Regulations (CFR) 52.4, these Guidelines prescribe the documentation and assurances that must accompany requests for NIH funding for research using human pluripotent stem cells from: (1) Awardees who want to use existing funds; (2) awardees requesting an administrative or competing supplement; and (3) applicants or intramural researchers submitting applications or proposals. NIH funds may be used to derive human pluripotent stem cells from fetal tissue. NIH funds may not be used to derive human pluripotent stem cells from human embryos. These Guidelines also designate certain areas of human pluripotent stem cell research as ineligible for NIH funding.

II. Guidelines for Research Using Human Pluripotent Stem Cells That Is Eligible for NIH Funding

A. Utilization of Human Pluripotent Stem Cells Derived From Human Embryos

1. Submission to NIH

Intramural or extramural investigators who are intending to use existing funds, are requesting an administrative supplement, or are applying for new NIH funding for research using human pluripotent stem cells derived from human embryos must submit to NIH the following:

a. An assurance signed by the responsible institutional official that the pluripotent stem cells were derived from human embryos in accordance with the conditions set forth in section II.A.2 of these Guidelines and that the institution will maintain documentation in support of the assurance;

b. A sample informed consent document (with patient identifier information removed) and a description of the informed consent process that meet the criteria for informed consent set forth in section II.A.2.e of these Guidelines;

c. An abstract of the scientific protocol used to derive human pluripotent stem cells from an embryo;

d. Documentation of Institutional Review Board (IRB) approval of the derivation protocol;

e. An assurance that the stem cells to be used in the research were or will be obtained through a donation or through a payment that does not exceed the reasonable costs associated with the transportation, processing, preservation, quality control and storage of the stem cells;

f. The title of the research proposal or specific subproject that proposes the use of human pluripotent stem cells;

g. An assurance that the proposed research using human pluripotent stem cells is not a class of research that is ineligible for NIH funding as set forth in section III of these Guidelines; and

h. The Principal Investigator's written consent to the disclosure of all material submitted under Paragraph A.1 of this section, as necessary to carry out the public review and other oversight procedures set forth in section IV of these Guidelines.

2. Conditions for the Utilization of Human Pluripotent Stem Cells Derived From Human Embryos

Studies utilizing pluripotent stem cells derived from human embryos may be conducted using NIH funds only if the cells were derived (without Federal funds) from human embryos that were created for the purposes of fertility treatment and were in excess of the clinical need of the individuals seeking such treatment.

a. To ensure that the donation of human embryos in excess of the clinical need is voluntary, no inducements, monetary or otherwise, should have been offered for the donation of human embryos for research purposes. Fertility clinics and/or their affiliated laboratories should have implemented specific written policies and practices to ensure that no such inducements are made available.

b. There should have been a clear separation between the decision to create embryos for fertility treatment and the decision to donate human embryos in excess of clinical need for research purposes to derive pluripotent stem cells. Decisions related to the creation of embryos for fertility treatment should have been made free

from the influence of researchers or investigators proposing to derive or utilize human pluripotent stem cells in research. To this end, the attending physician responsible for the fertility treatment and the researcher or investigator deriving and/or proposing to utilize human pluripotent stem cells should not have been one and the same person.

c. To ensure that human embryos donated for research were in excess of the clinical need of the individuals seeking fertility treatment and to allow potential donors time between the creation of the embryos for fertility treatment and the decision to donate for research purposes, only frozen human embryos should have been used to derive human pluripotent stem cells. In addition, individuals undergoing fertility treatment should have been approached about consent for donation of human embryos to derive pluripotent stem cells only at the time of deciding the disposition of embryos in excess of the clinical need.

d. Donation of human embryos should have been made without any restriction or direction regarding the individual(s) who may be the recipients of transplantation of the cells derived from the human pluripotent stem cells.

e. Informed Consent

Informed consent should have been obtained from individuals who have sought fertility treatment and who elect to donate human embryos in excess of clinical need for human pluripotent stem cell research purposes. The informed consent process should have included discussion of the following information with potential donors, pertinent to making the decision whether or not to donate their embryos for research purposes.

Informed consent should have included:

(i) A statement that the embryos will be used to derive human pluripotent stem cells for research that may include human transplantation research;

(ii) A statement that the donation is made without any restriction or direction regarding the individual(s) who may be the recipient(s) of transplantation of the cells derived from the embryo;

(iii) A statement as to whether or not information that could identify the donors of the embryos, directly or through identifiers linked to the donors, will be removed prior to the derivation or the use of human pluripotent stem cells;

(iv) A statement that derived cells and/or cell lines may be kept for many years;

(v) Disclosure of the possibility that the results of research on the human pluripotent stem cells may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development;

(vi) A statement that the research is not intended to provide direct medical benefit to the donor; and

(vii) A statement that embryos donated will not be transferred to a woman's uterus and will not survive the human pluripotent stem cell derivation process.

f. Derivation protocols should have been approved by an IRB established in accord with 45 CFR 46.107 and 46.108 or FDA regulations at 21 CFR 56.107 and 56.108.

B. Utilization of Human Pluripotent Stem Cells Derived From Human Fetal Tissue

1. Submission to NIH

Intramural or extramural investigators who are intending to use existing funds, are requesting an administrative supplement, or are applying for new NIH funding for research using human pluripotent stem cells derived from fetal tissue must submit to NIH the following:

a. An assurance signed by the responsible institutional official that the pluripotent stem cells were derived from human fetal tissue in accordance with the conditions set forth in section II.A.2 of these Guidelines and that the institution will maintain documentation in support of the assurance;

b. A sample informed consent document (with patient identifier information removed) and a description of the informed consent process that meet the criteria for informed consent set forth in section II.B.2.b of these Guidelines;

c. An abstract of the scientific protocol used to derive human pluripotent stem cells from fetal tissue;

d. Documentation of IRB approval of the derivation protocol;

e. An assurance that the stem cells to be used in the research were or will be obtained through a donation or through a payment that does not exceed the reasonable costs associated with the transportation, processing, preservation, quality control and storage of the stem cells;

f. The title of the research proposal or specific subproject that proposes the use of human pluripotent stem cells;

g. An assurance that the proposed research using human pluripotent stem cells is not a class of research that is ineligible for NIH funding as set forth in section III of these Guidelines; and

h. The Principal Investigator's written consent to the disclosure of all material submitted under Paragraph B.1 of this section, as necessary to carry out the public review and other oversight procedures set forth in section IV of these Guidelines.

2. Conditions for the Utilization of Human Pluripotent Stem Cells Derived From Fetal Tissue.

a. Unlike pluripotent stem cells derived from human embryos, DHHS funds may be used to support research to derive pluripotent stem cells from fetal tissue, as well as for research utilizing such cells. Such research is governed by Federal statutory restrictions regarding fetal tissue research at 42 U.S.C. 289g–2(a) and the Federal regulations at 45 CFR 46.210. In addition, because cells derived from fetal tissue at the early stages of investigation may, at a later date, be used in human fetal tissue transplantation research, it is the policy of NIH to require that all NIH-funded research involving the derivation or utilization of pluripotent stem cells from human fetal tissue also comply with the fetal tissue transplantation research statute at 42 U.S.C. 289g–1.

b. Informed Consent

As a policy matter, NIH-funded research deriving or utilizing human pluripotent stem cells from fetal tissue should comply with the informed consent law applicable to fetal tissue transplantation research (42 U.S.C. 289g–1) and the following conditions. The informed consent process should have included discussion of the following information with potential donors, pertinent to making the decision whether to donate fetal tissue for research purposes.

Informed consent should have included:

(i) A statement that fetal tissue will be used to derive human pluripotent stem cells for research that may include human transplantation research;

(ii) A statement that the donation is made without any restriction or direction regarding the individual(s) who may be the recipient(s) of transplantation of the cells derived from the fetal tissue;

(iii) A statement as to whether or not information that could identify the donors of the fetal tissue, directly or through identifiers linked to the donors, will be removed prior to the derivation or the use of human pluripotent stem cells;

(iv) A statement that derived cells and/or cell lines may be kept for many years;

(v) Disclosure of the possibility that the results of research on the human pluripotent stem cells may have commercial potential, and a statement that the donor will not receive financial or any other benefits from any such future commercial development; and

(vi) A statement that the research is not intended to provide direct medical benefit to the donor.

c. Derivation protocols should have been approved by an IRB established in accord with 45 CFR 46.107 and 46.108 or FDA regulations at 21 CFR 56.107 and 56.108.

III. Areas of Research Involving Human Pluripotent Stem Cells That Are Ineligible for NIH Funding

Areas of research ineligible for NIH funding include:

A. The derivation of pluripotent stem cells from human embryos;

B. Research in which human pluripotent stem cells are utilized to create or contribute to a human embryo;

C. Research utilizing pluripotent stem cells that were derived from human embryos created for research purposes, rather than for fertility treatment;

D. Research in which human pluripotent stem cells are derived using somatic cell nuclear transfer, *i.e.*, the transfer of a human somatic cell nucleus into a human or animal egg;

E. Research utilizing human pluripotent stem cells that were derived using somatic cell nuclear transfer, *i.e.*, the transfer of a human somatic cell nucleus into a human or animal egg;

F. Research in which human pluripotent stem cells are combined with an animal embryo; and

G. Research in which human pluripotent stem cells are used in combination with somatic cell nuclear transfer for the purposes of reproductive cloning of a human.

IV. Oversight

A. The NIH Human Pluripotent Stem Cell Review Group (HPSCRG) will review documentation of compliance with the Guidelines for funding requests that propose the use of human pluripotent stem cells. This working group will hold public meetings when a funding request proposes the use of a line of human pluripotent stem cells that has not been previously reviewed and approved by the HPSCRG.

B. In the case of new or competing continuation (renewal) or competing supplement applications, all applications shall be reviewed by HPSCRG and for scientific merit by a Scientific Review Group. In the case of requests to use existing funds or applications for an administrative supplement or in the case of intramural proposals, Institute or Center staff should forward material to the HPSCRG for review and determination of compliance with the Guidelines prior to allowing the research to proceed.

C. The NIH will compile a yearly report that will include the number of applications and proposals reviewed and the titles of all awarded applications, supplements or administrative approvals for the use of existing funds, and intramural projects.

D. Members of the HPSCRG will also serve as a resource for recommendations to the NIH with regard to any revisions to the NIH Guidelines for Research Using Human Pluripotent Stem Cells and any need for human pluripotent stem cell policy conferences.

Dated: August 17, 2000.

Ruth L. Kirschstein,

Principal Deputy Director, NIH.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Notification of Request for Emergency Clearance; Modification of OMB No. 0925–0001/Exp. 2/01, "PHS 398 Research and Research Training Grant Applications and Related Forms"

SUMMARY: In accordance with section 3507(j) of the Paperwork Reduction Act of 1995, the National Institutes of Health (NIH) hereby publishes notification of a request for Emergency Clearance for modification of the information collection related to the National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells, published elsewhere in today's **Federal Register**. The currently approved information collection OMB No. 0925–0001 permits the NIH to request from applicant institutions information related to application, award, and continued compliance with the terms of Federal assistance for research and research-related training. The approval also covers the information collection authorized in accordance with 42 CFR 52, specifically the obtaining of "[o]ther pertinent information the Secretary may require to evaluate the proposed project." (42 CFR 52.4(f))

The final National Institutes of Health Guidelines for Research Using Pluripotent Stem Cells requires submission of additional documentation in the form of additional institutional records from a limited number of institutions to enable an independent panel of non-Government experts to ascertain institutional compliance with the Guidelines. Compliance with the requirements of existing law and regulations is authorized under OMB No. 0925–0418, Exp. 1/01, "Protection of Human Subjects: Assurance Identification/Certification/ Declaration."

The present modification relates to the added reporting requirement of submission of documentation to permit the agency to exercise the oversight responsibility established under the Guidelines.

This modification is essential to the mission of NIH (42 USC 241 and 282(b)) and is of the highest scientific priority as determined by both internal review and external review by a panel of scientific and other experts in the field of stem cell research. After extensive consultation with the public and a public meeting, the NIH published proposed National Institutes of Health Guidelines for Research Using Human Pluripotent Stem Cells in the **Federal Register** on December 2 , 1999 (**Federal Register**, Vol. 64, No. 231, pages 67576–67579). The comment period was extended to February 22, 2000. (**Federal Register**, February 3, 2000, Vol. 65, No. 23, page 539). Following the period of comment, NIH has proceeded to finalize the Guidelines, which are published elsewhere in this issue of the **Federal Register**.

These Guidelines are essential to ensure that NIH-funded research in this area is conducted in an ethical and legal manner. The NIH has determined that the oversight process stipulated in the Guidelines will achieve this objective. The Guidelines will require that institutions requesting or using NIH funds for research using human pluripotent stem cells submit additional documentation to the NIH in the form of institutional records that will permit NIH oversight in accordance with the Guidelines.

NIH has taken all practicable steps to consult with the scientific community and the public, through the process described above and through the careful consideration of all comments received from the public.

In view of the extensive period of comment and the thorough consideration of all views, both prior to the publication of the proposed Guidelines in December 1999 and subsequently, NIH is herewith requesting that OMB approve the modification of the collection of information simultaneously with the publication of the **Federal Register**